R E M A R K S

Claims 1-24 are pending. The Examiner has offered the following grounds of rejection:

1. Certain claims stand rejected under 112, second paragraph as allegedly unclear with respect to the meaning of the phrase "providing a representation."

2. Certain claims stand rejected under 112, second paragraph as allegedly providing insufficient antecedent basis for the limitations "said first reference sequence" "said second reference sequence", "said acceptor heavy chain" and "said modified first complementarity-determining region."

3. Claims 1, 3-7, 9-13, 15-19, 21-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Aruffo ('693 patent).

4. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being obvious in light of Aruffo ('693 patent) and further in view of Hagiwara.

5. Claims 1-24 stand rejected under 103(a) as allegedly obvious in light of Jones *et al.* (Nature paper) and further in view of Yelton *et al.* (The Journal of Immunology 155:1994-2004 [1995]) and Soderlind *et al.* (Gene paper) and Hagiwara *et al.* (US Patent No. 5,589,573, issued Dec. 31, 1996).

6. The oath is allegedly defective.

7. Certain typographical problems with the claims have been raised.

8. The amendment to page 65 has been questioned.

1. The Claims Are Clear and Definite

Certain claims stand rejected under 112, second paragraph as allegedly unclear with respect to the meaning of the phrase "providing a representation." Applicants disagree. Speaking generally (and not with regard to the specific invention), the art recognizes that one can work with the physical nucleic acid - or one might work with a representation of the physical nucleic acid. Speaking now specifically about the present application, Figure 1 is a representation of sequences. Figure 1 is a representation, in that it provides art-recognized symbols[1] for the sequence. Moreover, Figure 1 is an alignment such as might be used in a manner taught in the claims (e.g. "wherein said framework positions that are changed are selected from among said acceptor framework positions of said second reference sequence that differ . . .") because alignments facilitate such comparisons to determine differences. Figure 1 is discussed (see page 51 of the specification) in a manner that makes it clear to the reader that Figure 1 is a representation of sequences. In the case of certain embodiments of the present invention, there are advantages to working with representations of nucleic acid rather than the physical nucleic acid.

Moreover, overlapping oligos were synthesized to construct/encode VH and VL of murine anti-CD40, "*based on the sequence* of anti-CD40 murine mAb 40.2.220." (emphasis added). From this, it is clear to one skilled in the art that a representation (whether hard copy or electronic copy) of the referenced sequence was used to design the overlapping oligos.

While the term "representation" is clear, applicants have amended the claims to further clarify that the representation is (like Figure 1) a "visual" representation, i.e. symbols that are visible to the eye (whether on a computer screen or on a piece of paper). This amendment is made to further the prosecution and applicants hereby reserve the right to prosecute the unamended claims in the future.

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[1] Webster's College Dictionary (Random House 1991) notes that a representation is an "expression or designation [using a] . . . character, symbol, or the like." Thus, a representation is more than a "thought pattern."

2. There is Proper Antecedent Basis

Certain claims stand rejected under 112, second paragraph as allegedly providing insufficient antecedent basis. Applicants do not agree and believe that the claims are clear as previously submitted. Nonetheless, to further the prosecution, and without waiving the right to prosecute the unamended claims in the future, the claims have been amended to make clear the distinction between "donor" and "acceptor" sequences. In addition, amendments have been made to make it clear that, in certain instances, comparisons are being made between the visual representations and what is encoded by what is synthesized (this addresses item 8d on page 4 of the Office Action).

3-4. The 131 Declaration Removes the Arrufo Patent

The Examiner maintains that the '693 patent is 102(e) prior art. MPEP section 715 notes the appropriateness of swearing behind a 102(e) reference in these circumstances. The attached 131 Declaration of Dr. Watkins notes that he is a co-inventor on the Aruffo patent and points out that the very sections cited by the Examiner (regarding the overlapping oligo work) track language in the present specification. In sum, it is the same work and clearly must have been completed prior to the February 1999 filing date (or otherwise could not have been included in the '693 filing). For this reason, there is no need for notebook data or the like (as noted in MPEP 715, such data is not necessary where a satisfactory explanation is provided). If view of the 131 Declaration, the rejections based on the '693 patent [both the 102(e) rejection and the 103(a) rejection] must be withdrawn.

5. The Claimed Embodiment Is Not Obvious

The Examiner alleges that the claims are obvious and unpatentable over Jones *et al.* and further in view of Yelton *et al.* (The Journal of Immunology 155:1994-2002 [1995]) and Soderlind (Gene paper) and Hagiwara *et al.* (US Patent No. 5,589,573, issued 12/1996). Applicants cannot agree. There is no proper basis for the combination of the cited art. Moreover, even if the art is (improperly) combined, all of the elements of the presently pending claims are not taught.

A. There Is No Basis For The Combination

To establish *prima facie* obviousness, the Examiner must point to some motivation or suggestion within the references themselves, or within the knowledge generally available to one of ordinary skill in the art at the time of invention, to combine or modify the references. *See* MPEP §2143.01; *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Merely because the references ***could be*** combined or modified does not render the resultant combination obvious unless the prior art suggested the combination. MPEP §2143.01; *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990).

Applicants submit that the references cannot be considered collectively until the Examiner points to ***some motivation to combine*** those references. The purpose behind this requirement is to prevent the Examiner from using the invention itself and hindsight reconstruction to defeat the patentability of the invention. The Federal Circuit, in a recent decision, articulates this position:

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

See In re Rouffet et al., 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). It is readily apparent that the law of *In re Rouffet* requires the Examiner to present soundly reasoned arguments based upon the substance of the cited references.[2] Moreover, the law does not regard the Examiner as one skilled in the art. *See In re Rijckaert*, 28 USPQ2d 1955 at 1956 (Fed. Cir. 1993)("[T]he examiner's assumptions do not constitute the disclosure of the prior art."); *See id.* at 1957 ("[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears."). Indeed, the Federal Circuit has made it clear that "[b]road, conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence.'" *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614 (Fed. Cir. 1999).

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[2] *Accord Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (stating that the examiner must present convincing line of reasoning supporting rejection).

1. Jones *et al.* Do Not Recognize The Problem

The Examiner argues that motivation is found "because Jones et al teach CDR grafting onto a human framework and the antibody has a *lower* affinity than the murine antibody . . ." (Office Action, page 8, emphasis added). But wait! The Jones et al. paper does NOT recognize the lower affinity as a *problem*. The Examiner is asked to note that the Jones reference boasts that after merely grafting, "the new antibody has acquired the hapten affinity" of the mouse antibody (see the Abstract of the Jones paper). Later in the paper (see the text across from Table 1), the results are summarized:

> ". . . the difference in affinity is less than expected for loss of either a hydrogen bond or van der Waals' contact from the active site of an enzyme. Thus, it seems that binding affinity and specificity for hapten can be conferred on a human antibody by grafting in the CDRs from an appropriate mouse antibody."

Thus, Jones *et al.* are not identifying a problem that needs to be fixed.[3] Jones *et al.* is clearly teaching that grafting is all that is needed to confer binding affinity. Therefore, there is no justification in combining the Jones *et al.* paper with antibody maturation papers, since there is no suggestion or teaching that further manipulations are necessary.

2. Hagiwara Is Not An Antibody Engineering Reference

A review of Hagiwara reveals that it is not an antibody engineering reference, merely an antibody cloning reference with no apparent teaching to make changes in the sequence. Why would one skilled in the art combine such disparate art and techniques? The Examiner is reminded that there are many techniques in use.

3. Yelton Cautions That Higher Affinity May Not Be Advantageous

The Examiner argues that "Yelton et al teaches affinity maturation of an antibody . . ." (Office Action, p. 7). But the Examiner fails to take note that Yelton cautions that higher affinity may not be advantageous:

> "The range of Ab affinities best suited for optimizing the potency and efficacy of Ab-targeted therapeutic agents is controversial. Mathematical and computer models . . . have suggested that increasing the affinity of an Ab may not bring a therapeutic advantage."

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[3] The Examiner is reminded that "a patentable invention may lie in the discovery of the source of the problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103." *In re Sponnoble*, 160 USPQ 237, 243 (CCPA 1969). MPEP 2141.02.

Moreover, Yelton et al. cannot be offered as a reference that teaches grafting always creates a problem that needs to be solved with changes to the CDR. The Examiner should note that Yelton deals with a *particular* antibody with lower affinity. Importantly, Yelton does not teach that one should simply assume lower affinity at the time of grafting and make CDR changes at that time.

Finally, Yelton *et al.* use the method of Kunkel *et al.* for the mutagenesis strategy, which does not involve the use of populations of overlapping oligonucleotides. Why would one skilled in the art combine the teachings of Yelton with a reference that teaches a different technique for mutagenesis?

4. Soderlind Does Not Attempt To Retain Antigen Binding

The Examiner argues that "Soderlind et al teach libraries of variable domains wherein the CDRs are mutagenized . . ." (Office Action, p.7). But the Examiner has apparently overlooked the fact that Soderlind *et al.* admits they are taking a completely different approach:

> "Instead of depending on in vivo preformed Ab specificities found in gene libraries, we have investigated an alternative route . . ."

Thus, Soderlind is not utilizing a donor sequence with known specificity for an antigen even as a reference point! There is certainly no reason to combine any elements of Soderlind with any of the other references. This is a case of apples and oranges.

B. Even If (Improperly) Combined, All Elements Are Not Taught

It has been argued above that the Examiner has no basis for combining the disparate references and their disparate techniques. Therefore, no prima facie case of obviousness has been established.[4] Without waiving that argument, it is pointed out here that - even if improperly combined - the references do not teach the embodiment claimed.

In this regard, the Examiner is requested to note that step "D" of Claim 1, for example, specifies combining the nucleic acid coding for acceptor frameworks with nucleic

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[4] "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant . . . . If examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent." *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

acid coding for modified *donor* CDR sequences. The use of the donor sequences together with acceptor frameworks is the "grafting" element of Claim 1; the modification of the donor CDR sequences is the reacquisition of affinity element of Claim 1.

The present specification notes (at page 17, lines 19-25) the advantages of combining these elements into a single step:

> "[In prior art approaches]. . . once the CDR-grafted antibody, or variable region binding fragment is made, it requires subsequent rounds of molecular engineering to reacquire binding affinity comparable to the donor antibody. The present invention combines these steps such that CDR grafting and binding reacquisition occur in a single simultaneous procedure."

At no point in Jones *et al.* or in Yelton *et al.* is it taught that these two *procedures* are to be performed in one step.

Thus, the Examiner's combination of art - even if improperly made - does not supply the elements presently claimed. On this basis alone, the Examiner's rejection must fail.

6-8. Typos and Formal Issues

The oath is allegedly defective. New documents are submitted herewith. Certain typographical problems with the claims have been raised. The amendments address these formalities. Finally, the amendment to page 65 has been questioned. Applicants apologize for the confusion. While the page numbering was problematic, the intent was to replace the Abstract with new text.

CONCLUSION

Applicants believe that the arguments set forth above traverse the Examiner's rejections and therefore request that these grounds for rejection be withdrawn for the reasons set forth above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (617)-984-0617.

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